REMARKS/ARGUMENTS

This Amendment is filed after Applicant had filed a Notice of Appeal and filed an Appeal Brief in the above entitled matter. The response to the Appeal Brief has been to withdraw the Appeal, cite new references including the new secondary references to Kachigan (5;084,005) disclosing a spherical swab and Wach et al.(6,174,424) disclosing fiber optical couplers having shapes similar to those set forth in this disclosure, and institute a first Office Action rejecting the invention claimed in the Appeal Brief.

There remains a fundamental point of disagreement between Applicant and the Examiner. The question is whether the so-called Third Embodiment of Liotta et al. teaches a rod or probe? Applicant takes the position that a rod or probe is not taught. The Examiner takes the position that a rod or probe is taught (see page 3 of the Office Action of September 4, 2003) or that whether a rod or probe is taught is irrelevant (see last partial paragraph, page 5 Office Action).

In what follows, Applicant will summarize the article as claimed; an activatable surface is placed at the end of a rod on a convex surface. This enables placement of a dissected sample at numerous closely spaced areas on the convex surface. Specifically, the utility of the claimed article is that as sample is gathered, simple rotation of the rod exposes different areas of the rod for sample dissection and collection.

Next, Applicant will paraphrase the rejections contained in this Office Action. The rejections will be repeated both as to the art as applied and to the Examiner's critique of applicant's previous arguments (including those in the Appeal Brief).

Thereafter, Applicant will quote English definitions including "probe", "rod", "activate", and "convex" from a contemporary source (Microsoft Encarta Dictionary).

Applicant will summarize Liotta et al. (the principal reference herein) in the same manner as he did in his Appeal Brief. Specifically, it will be urged that the so-called "Third Embodiment" of Liotta et al. does not include or suggest either a probe or a rod. This is a central disagreement with the Examiner's interpretation of this Liotta et al. reference.

Finally, the new references cited by the Examiner will be distinguished. Specifically, the argument will be made that a swab or optical fiber acts in a completely different manner than the convex surface covered with activatable material. This will necessitate referring to the definition of a "swab" from a contemporary dictionary. It will be pointed out that the reference to the swab differs completely from an activatable coating on a convex surface. Regarding the reference to the optical couplers, fibers emitting or receiving light have nothing to do with the captured dissection technique herein disclosed. Law will be cited to effect that the references utilized neither show nor suggest the cited combination of obviousness. Patentability will be urged.

Inventions Summarized

An apparatus for laser capture microdissection is disclosed having a contact surface for contacting the sample undergoing the microdissection. First, there is a convex surface for placement to a sample. Second, a rod is utilized with the convex surface mounted to an extremity of the rod. Finally, a selectively activated coating is placed over the convex surface having non-adhesive properties to a sample which can be activated to provide selected regions thereof with adhesive properties to a sample when placed to the sample. The nonactivated regions of the selectively activated coating remain with the nonadhesive properties. This is the invention set forth in independent claim 35.

In the independent claims 41, an apparatus for laser capture microdissection including a contact surface and vial is claimed. First, there is a convex surface. A selectively activated coating is placed over the convex surface having non adhesive properties which can be activated to provide selected regions thereof with adhesive properties when placed to a sample while non activated regions thereof remain with the nonadhesive properties. Finally, a vial having a dimension for permitting the convex surface to be placed into the vial is utilized. Finally, a fluid is placed in the vial for liberating at least part of the tissue sample adhered to the selectively activated convex surface. It is readily seen that once sample is collected (and

concentrated) to the convex surface at many different points, the sample can be liberated to solution in the vial.

Rejections Summarized

First, claims 35, 36, 38, 40 and 41 are all rejected under 35 USC 103(a) has been unpatentable over Liotta et al. (5,843,657) in view of Kachigan (5,084,005). The rejection of the Examiners states "Liotta teaches a method and apparatus for microdissection of tissue samples which utilizes a probe with a selectively activatable transfer surface for adhering to cells of interest. The probe is that shown in Figures 8A-8D and described in columns 12 and 13." (Emphasis added.)

This portion of the Liotta et al. reference is what Applicant will later summarize as the "Third Embodiment" of Liotta. This is where Applicant and the Examiner have their disagreement; Applicant takes the position that a probe is not shown nor suggested, the Examiner takes the position that a probe is either shown or whether it (the probe) is shown or not is irrelevant. Applicant notes that in the rejection of claims 35, 36, 38, 40 and 41, in describing this Third Embodiment of Liotta et al., the Examiner uses the term "probe" six times.

Second, claims 37 and 39 are all rejected under 35 USC 103(a) over the above references with the addition of Wach et al. (6,174,424). Wach et al. relates to manufacturing couplers for optical fibers; some of the couplers happen to have "a faceted convex surface and a convex surface within the profile of a frustum." Applicant questions how this combination is logically made.

In Response to Arguments (of Applicant contained in the Appeal Brief), the Examiner in citing the spherical (convex) swab of Kachigian sets forth that this provides "the convex surface that Liotta does not teach."

Regarding the Second Liotta Embodiment of Liotta, the Examiner agrees with the Applicant that a selectively activatable coating is not taught.

Third, regarding the "Third Liotta Embodiment" (as labeled by Applicant on page 13 of the Appeal Brief (and repeated in this Amendment)) the Examiner does not agree that

Liotta is different from the instant invention because "it is not a probe." In the exact words of the rejection, "applicant has claimed an apparatus with a contact surface comprised of a rod with a convex surface attached with a selectively activated coating...- not a probe." As will hereinafter be shown, the terms "probe" and "rod" are almost indistinguishable.

The Examiner then incorporates into his action that portion of the Liotta et al. specification from paragraphs 52 through 62 which are descriptive of what Applicant has chosen to label the "Third Liotta Embodiment." Applicant notes that this description does not include the equivalent of a "probe" or "rod" anywhere; instead, the terms "transfer surface 30" and "backing layer 31" (the backing layer being the support for the transfer surface) are used.

The Examiner then makes a statement to which the Applicant agrees. "The Examiner believes this (paragraphs 52 through 62) is a clear teaching of a selectively activatable adhesive layer used in transferring tissue as shown in the Figures 8A-8D." Applicant does not agree that a "probe" or "rod" is shown or suggested in anyway.

Plain Language Definitions

Applicant provides the definitions of "probe," "rod," "activate," and finally "convex."

For the purposes of this Amendment is submitted that the terms "probe" and "rod" are virtually indistinguishable as evidenced by the following definitions:

rod [rod] (plural rods)
noun
1. thin stick: a narrow, usually cylindrical, length of wood, metal, plastic, or other material.

probe [prōb]
noun (plural probes)

3. surgery dentistry surgical instrument for exploring: a long thin instrument used by doctors and dentists for exploring or examining

To complete the meaning of the claim, the terms "convex" and "activate" are defined as follows:

con·vex

adjective

1. outwardly curving: with a surface that curves outward rather than inward

ac·ti·vate [áktə vàyt] (past ac·ti·vat·ed, past participle ac·ti·vat·ed, present participle ac·ti·vat·ing, 3rd person present singular ac·ti·vates)

verb

1. transitive verb making something active: to make something active, or set something in motion;

2. intransitive verb become active: to become active or begin to operate;

3. transitive verb physics make something radioactive: to make something radioactive;

4. transitive verb chemistry to make something reactive: to increase the rate of a chemical reaction, for example, by applying heat;

5. transitive verb chemistry to increase power of adsorption: to treat a substance such as charcoal so as to increase its capacity for adsorption.

(All definitions in this Amendment are taken from the Microsoft Encarta Dictionary.)

The Three Embodiments of Liotta et al.

Liotta et al. filed US Patent Application #08/203780 on March 1, 1994 which subsequently issued as United States Patent 5,843,644 on December 1, 1998. This patent disclosed the first and second embodiments set forth in Liotta et al. United States Patent 5,843,657. Taken from applicant's Appeal Brief, these first and second embodiments can be summarized as follows:

First Liotta Embodiment

First, and referring to Fig. 3, conventional dissection of a sample (1) utilizing a cutting blade (10) and grasping arm (11) is disclosed.

Both the Examiner and the applicant agree that this part of Liotta et al. '657 is not relevant to the rejection.

Second Liotta et al. Embodiment

Second, and referring to Figs. 2a to 2c, the use of a "sticky contact probe" is set forth for dissection of a sample (1) at a target sample zone B. In short, a contact probe (5) is provided. The end of the contact probe is provided with adhesive/extraction reagent (6). The contact probe (5) at the adhesive/extraction reagent (6) is contacted to the target sample zone B, the sample zone B adheres to the reagent (6) and is dissected and removed with the probe as the probe is removed.

There is an important limitation on the use of the "sticky contact probe." This limitation is provided at column 4, lines 35 through 41 of the Liotta et al. specification as follows:

> ... As can be readily understood from Fig. 2a, the surface area of the contact probe tip (and the adhesive-extraction reagent) needs to be about equal to, and no greater than, the surface area of the

zone to be extracted. Otherwise, excessive removal of adjacent tissue zones will occur.

This part of Liotta et al. ' 657 is relevant for the use of the probe. Since the probe does not have a "selectively activatable surface" it is sticky all of the time. When it contacts portions of the specimen it adheres.

The probe is flat at its end; it cannot be said to have a "convex" surface. Further, the size of the end of the probe is restricted as it is always sticky; it has to be less than "the surface area of the zone to be extracted." In other words, when the probe from this embodiment of Liotta et al. ' 657 is used as a reference, the limitation of the probe's use must follow. Finally, adhesive/extraction reagent is only placed at the flat end of the probe. It is not disclosed as being at any other part of the probe.

Both the Examiner and Applicant agree that the "Second Liotta Embodiment" is not relevant to this invention. This however, is the only embodiment of Liotta et al. which discloses anything like a "probe" or "rod". It is to be noted that the "Third Liotta Embodiment" never appears in the Liotta et al. US Patent 5,843,644 issued on December 1, 1998.

Liotta et al. then proceeded to discover the utility of what later came to be known as laser capture microdissection, now a fairly generic technique utilized in dissecting extraordinarily small samples of material, such as cancer cells, from specimens. Having made this discovery, Liotta et al. filed Patent Application Serial Number 08/544388 on October 10, 1995 as a Continuation-in-Part. Because of this addition, Dr. Robert F. Bonner was joined as in the inventor in the Continuation-in-Part Patent Application. This patent issued as United States Patent 5,843,657 on December 1, 1998. This patent is the principal reference herein and contains all three Liotta embodiments.

For the first time, the Third Liotta Embodiment was disclosed in that Application. For convenience, a summary of that disclosure is taken from applicant's Appeal Brief:

Third Liotta et al. Embodiment

Third, and referring to Figs. 8a to 8d, the first disclosure of laser capture microdissection is set forth. This material was added with the CIP that resulted in the cited reference.

A transfer surface (30) is utilized to extract targeted cellular material from cellular material (33) residing on support member (34). Initially in Fig 8a, transfer surface 30 having upper backing layer 31 and a lower activatable adhesive layer 32 overlies cellular material 33 residing on support member 34. Secondly in Fig 8b, contact occurs between the transfer surface 30 and the sample 33. Thirdly in Fig 8c, the transfer surface 30 is irradiated with a laser beam 36 overlying that part of the sample 33 where extraction is desired. Unlike the second Liotta embodiment where the probe is always sticky, this portion of the transfer surface (which is not a probe), only becomes sticky on "activation." Fourthly in Fig 8d, transfer layer 30 is lifted; an adhered portion of the sample 33 is dissected.

This part of Liotta et al. '657 is relevant for the use of the transfer surface. Applicant points out (and the Examiner disagrees) that this embodiment has nothing to do with the use of a probe.

Article Invention Summarized

The disclosure herein can be best understood with respect to Fig 4A of the specification herein. Simply stated, and utilizing the original Liotta et al. disclosure (Third Liotta Embodiment), a person collecting a sample had two choices. First, he could collect the dissected sample on the transfer surface in the same spatial relation as the dissected sample was found on the sample. Alternatively, by moving the sheet so as to juxtapose the adhered sample portion with a sample portion to be extracted, dissected specimen concentration could be achieved.

There was a disadvantage to this concentration technique when a sheet was used. Simply stated, the dissected sample portion on the sheet would likely contact the sample. Nonspecific transfer (wanted portions of sample with unwanted portions of sample) could occur. Moreover, extracted and dissected specimen already on the transfer layer would be contacted to specimen as additional portions of the specimen were dissected. What was needed was a way to collect and concentrate dissected specimen.

The solution to this was to place the activatable material on a convex surface. Concentration of the individual specimen portions would occur. This concentration would occur in a manner precisely identical to that illustrated in Figs 4A and 4B. In making this assertion, Applicant realizes he is not claiming the process there illustrated; but he does choose to claim the article there illustrated.

Summary of the Relevant References

Liotta et al. has previously been summarized; its teachings will not be repeated here.

Kachigian United States Patent 5,084,005 relates to a swab. That swab is never going to be able to have the appearance set forth in Figs 4A and 4B. This can be understood from the plane dictionary meaning of the word "swab" (again taken from the Microsoft Encarta Dictionary.)

> swab [swob]
>
> noun
>
> 1. surgery soft material for mopping up blood: a small piece of gauze, cotton, or other soft material, used to mop up blood during surgery;
>
> 2. medicine small stick with cotton: a small stick, wire, or plastic wand with cotton attached to one or both ends, often used to clean wounds, apply medicine, or obtain a specimen of something;

> 3. medicine specimen: a specimen of mucus or another secretion obtained by using a swab.

First, reviewing Figs 4A and 4B, the difference between the convex surface being part of a swab and being covered with the activatable material here illustrated is apparent. A swab does not have the characteristic of isolating portions of the same specimen the manner shown in these figures. Swabs operate by capillary action; specimen taken at one portion of the swabs freely intermingles with specimen taken at other portions of the swab. Additionally, and referring to page 13 of the specification herein, sufficient amounts of the desired cells can be collected for analysis, these cells once collected are concentrated, and once collected and concentrated can be subjected to inspection before further processing. No swab can accomplish this concentration and inspection with respect to taking more than one sample.

Regarding, Wach et al. US Patent 6,174,424, although this patent is cited for the various shapes at the end of the fibers utilized, it is not seen how this type device is relevant with respect to that shown in Figs 4A and 4B. Specifically, although the shape is shown, there is no motivation for the combination of the references. Why would one look to optical fibers at their light emitting and/or receiving ends for shaping a dissecting probe?

Applicable Law

The rejection, in the effort to find the right shape for a collection and dissecting device, selects shapes from completely nonanalogous collection devices without ever asking, what is the motive for the combination? This leads into common errors typically found in these kinds of rejections. As set forth in *Hodosh v. Block Drug Co., Inc.* (CA FC; 1986), 229 USPQ 182, at Footnote 5.:

> Our comments on the district court's obviousness determination generally include the following tenets of patent law that must be adhered to when applying §103: (1) the claimed invention must be

> considered as a whole (35 USC 103; see, e.g., Jones v. Hardy, 727 F.2d 1524, 1529, 220 USPQ 1021, 1024 (Fed. Cir. 1984) (though the difference between claimed invention and prior art may seem slight, it may also have been the key to advancement of the art)); (2) the references must be considered as a whole and suggest the desirability and thus the obviousness of making the combination (see, e.g., Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984); (3) the references must be viewed without the benefit of hindsight vision afforded by the claimed invention (e.g., W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983)); (4) "ought to be tried" is not the standard with which obviousness is determined (Jones, supra, 727 F.2d at 1530, 220 USPQ at 1026); . . . .

Judged against these standards, what is the motive for the combination of the shape of a swab and a selectively activated surface? What is the motive for the combination of an optical fiber having a particular shape, a spherical swab, and a selectively activated surface? Applicant submits that there is no motive.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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